Original Article

Effects of Methadone on Liver Enzymes in Patients Undergoing Methadone Maintenance Treatment

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Abstract

Background: Methadone is currently the most frequently used substance in the treatment of short-term and particularly long-term opiate dependence. Patients' beliefs about the adverse effects of methadone on function of organs, especially liver, have widely affected the use of this substance. This study aimed to determine the effects of methadone on liver enzyme levels in patients on methadone maintenance treatment.

Methods: In a retrospective study, a total of 94 patients undergoing methadone maintenance therapy were recruited from Shahid Beheshti Hospital (Kerman, Iran). Liver enzyme levels in all patients were tested every six months from the onset of treatment until 24 months. The relations between test results and age, gender, and methadone dose were then evaluated. Data was analyzed using logistic regression with random data plan.

Findings: At the 24th month, alanine aminotransferase (ALT) levels in 4 patients (4.3%) and aspartate aminotransferase (AST) levels in 3 patients (3.2%) were above normal. Among 46 patients (50.0%) who had normal alkaline phosphatase (ALP) levels after 24 months, 26 subjects were younger than 40 and 20 subjects were over 40 years of age. The mean age of subjects with abnormal ALP levels and the mean methadone dose were 39.9 years and 19.55 cc, respectively.

Conclusion: The results of this study indicated the significant effect of methadone on ALP levels. These effects can account for cholestatic pattern liver injury (obstruction). Further prospective studies including greater samples of patients with heart and liver complications and encompassing other drugs are required to confirm our findings.

Keywords: Methadone, Substance abuse, Liver, Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase

Addict Health 2012; 4(3-4): 111-116.
Received: 22.02.2012, **Accepted:** 20.05.2012

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Introduction

Opiate abuse and dependence is a complex, multidimensional problem. In a survey by the Iranian Ministry of Health in 2004, in male gender, addiction was the second cause of years lost due to disability after accidents.[1,2] Injection substance abuse is a major public health concern with side-effects including human immunodeficiency virus (HIV) and hepatitis infections. Detoxification or medically managed withdrawal programs alone are not considered as an effective treatment for dependence to opiates including heroin.[3] Oral methadone is currently recognized as the international method for treating heroin dependence. Methadone removes or minimizes withdrawal symptoms and thus reduces reliance on heroin. Methadone is effective for 24 hours and can act as a substitute for 3-5 times of heroin consumption (short long effect). Moreover, methadone blocks the euphoric effects of heroin and thereby helps reduce patients' craving.

Overall, methadone has been recognized as the most effective researched substance for the treatment of opiate-dependent patients.[4] Methadone is metabolized in the liver by cytochrome P450 and its metabolite is secreted in urine. Women metabolize methadone more rapidly compared to men. Following oral administration, methadone has an initial half-life of 12-24 hours and a secondary half-life of 55 hours.[5,6]

There is a widely held assumption about the adverse effects of methadone. However, few reports, including two studies in the 1960s on only three patients whose history prior to methadone treatment was not available, have actually confirmed such adverse effects.[7,8] In a prospective study conducted by Kreek et al. in 1972, a total of 129 heroin-dependent patients on methadone maintenance treatment (using 80-120 mg of methadone) were evaluated for three years. The researchers found no substantial evidence to support liver toxicity by methadone and postulated that hepatitis and alcohol overconsumption may be the possible factors leading to liver dysfunction in these patients.[9] In another study conducted in New York, patients consuming high doses of methadone following alcohol and barbiturate overdoses were tested. In 7% of the subjects, increased levels of alkaline phosphatase (ALP) were observed but restored to normal after a given time.[10] In Iran, Tashakori et al. evaluated 98 addicts (71% heroin-dependent, 7 HIV positive subjects) undergoing methadone maintenance treatment. They reported liver function values to remain normal during the year following methadone treatment. In hepatitis C virus (HCV) positive patients, however, the values elevated shortly after treatment and then remained moderate during the remainder of the course. The researchers thus stated that methadone may be hepatotoxic in HCV positive patients and should be used with caution in these patients.[11] Although very few studies have indicated the effects of HCV infection on methadone serum levels, a number of researchers have suggested methadone to be used with monitoring of methadone serum levels in HCV positive patients.[12]

There are several noninvasive laboratory tests to assess liver. Repeated application of these tests can detect alteration in liver function and evaluate specific patterns of liver dysfunction. However, although these tests are capable of distinguishing between viral hepatitis and cholestatic syndromes, they cannot be used as a pathognomonic test for a certain liver disease.[13] These tests are not highly sensitive and may exhibit normal findings in patients with severe liver disease. However, in evaluating the severity of disease, these tests can contribute to other data in predicting disease prognosis.[14] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and their ratio are the most frequently used tests in liver function assessment. Elevated levels of ALT and AST indicate their release from tissues rich in these enzymes. Such an event may suggest liver cell death. Tissues rich in AST include liver, heart, skeletal muscles, pancreas, and lungs. ALT is normally found in liver and kidneys. High levels of these enzymes are nevertheless not necessarily indicative of liver damage or necrosis. Elevations of these enzymes up to 8 folds of their normal limits are non-specific and can be seen in any liver disease or specific clinical populations.[15] Most elevations are observed in hepatocellular damage such as alcohol hepatotoxicity and viral hepatitis. Since in acute or chronic liver conditions, enzyme elevations may not be persistent over time, a single test cannot determine the degree of liver disease.[6] Elevated alkaline phosphatase levels may suggest cholestasis or liver infiltration.[16]

Studies on hepatotoxicity of methadone have

been very few and brief. Therefore, given the increasing population of patients on methadone treatment in Iran, this retrospective study aimed to measure AST, ALT, and ALP levels in patients on methadone maintenance treatment prior and two years following the onset of treatment. It also tried to determine alterations in the mentioned variables with respect to age, gender, and dosage of methadone.

Methods

In a retrospective study, a total of 94 patients undergoing methadone maintenance treatment in Shahid Beheshti Hospital (Kerman, Iran) were recruited. Written consents were obtained from patients to use their hospital records in the study. Patient records included demographic characteristics, initiation date of methadone maintenance treatment, dates of visits, and dosage of methadone used. Liver enzyme levels including ALT, AST and ALP levels were tested at the onset of methadone maintenance treatment and every 6 months for a period of 24 months. The results of the final test were registered in patient records.

Patients were included if they had been on methadone maintenance treatment for at least one year since this trial also lasted for a year. Methadone dosage was determined by the clinic's physician based on the amount of opiate used by the patient. The main variables were defined and enzyme alterations were demonstrated using linear graphs. Linear regression models were then used to evaluate the effects of the main variables, i.e. time and dosage of methadone. Stata software was used to analyze these models and random effect was employed to counteract the effects of repeated testing. For data analysis, logistic regression model with random data patterns was utilized.

Results

Of the 94 participants, 92 (97.9%) were men and two were women. The mean age of patients and the mean daily dosage of administered methadone were 40.9 years (range: 21-62 years) and 19.4 cc (range: 1-64 cc), respectively. Liver enzymes were found to be normal prior to the 24th month. After that however, half of the patients exhibited elevated ALP levels. Abnormal AST and ALT levels were also detected in 4 (4.3%) and 3 (3.2%) patients, respectively (Table 1).

As apparent from table 2, patients with abnormal ALP levels had a mean age and a mean methadone dosage of 39.9 years and 19.5 cc, respectively. The corresponding values were found to be 54.3 years and 16 cc in patients with abnormal AST levels and 50.3 years and 15 cc in patients with elevated ALT levels. Abnormal liver enzyme levels were not found to be significantly associated with age or methadone dosage.

Patients were classified as younger than or equal to 40 years old and over 40 years of age. Of the patients with abnormal ALP levels, 26 were below 40 years old and 20 patients aged over 40. Of the total 92 patients, 46 patients were found to have abnormal ALP levels in month 24. At the final measurement, 50 patients aged ≤ 40 years old and 43 patients aged > 40 years of age. One patient younger than 40 years had missing data (ALP level was not measured at the 24th month). Therefore, out of 92 patients with complete data, 46 patients, all of whom were male, exhibited positive results in month 24.

Table 1. Frequency and 95% confidence interval (CI) of positive samples for alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

	ALT			AST			ALP		
	Percent (95% CI)	Positive	Number	Percent (95% CI)	Positive	Number	Percent (95% CI)	Positive	Number
Baseline	-	0	85	-	0	85	-	0	86
6th month	-	0	51	-	0	51	-	0	51
12th month	-	0	55	-	0	55	-	0	53
18th month	-	0	54	-	0	54	-	0	54
24th month	3.2 (0-6.8)	3	93	4.3 (0.36-8.2)	4	93	50.0 (40.0-60.0)	46	92

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; CI: Confidence intervals

Table 2. Patients' age and methadone dose based on the defective enzyme

Enzyme (u/l)		Index	Range	Mean ± SD
ALP	Normal (25-112)	Age (years)	21-59	39.9 ± 9.5
		Dose (cc)	4-45	19.5 ± 8.5
	Abnormal	Age (years)	21-62	41.2 ± 9.1
		Dose (cc)	1-64	18.9 ± 11.3
AST	Normal (10-44)	Age (years)	53-56	54.3 ± 0.5
		Dose (cc)	13-21	16.0 ± 4.4
	Abnormal	Age (years)	21-62	40.1 ± 9.1
		Dose (cc)	1-64	19.0 ± 10.9
ALT	Normal (10-31)	Age (years)	38-56	50.3 ± 8.3
		Dose (cc)	12-21	15.0 ± 4.1
	Abnormal	Age (years)	21-62	40.8 ± 9.2
		Dose (cc)	1-64	19.0 ± 11.0

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

Four male patients (4.3%) (one younger than 40 years old) were found to have abnormal ALT levels in month 24. The numbers of patients with complete ALT test results at baseline and after 6, 12, 18, and 24 months were 86, 51, 55, 54, and 93, respectively. The corresponding numbers of patients with complete AST test results were 85, 51, 55, 54, and 93. Only three patients (3.2%), all of whom aged over 40, exhibited abnormal AST levels in month 24. In patients with abnormal ALT, three patients received less than 20 cc of methadone while one subject received over 20 cc. On the other hand, two and one patients with abnormal AST levels received < 20 cc and > 20 cc of methadone, respectively.

Discussion

In the present study, half of the patients exhibited abnormal ALP levels at the end of the study (month 24). Abnormal AST and ALT levels were found in 4.3% and 3.2% of the patients, respectively. Despite the small sample size, the observed levels may indicate the cholestatic pattern of liver injury (obstructive) due to methadone. This pattern is mainly caused by drugs suppressing bile secretion from the liver. Despite the higher prevalence of hepatitis B and C in addicts and the subsequent liver enzyme elevations, lack of ALT and AST elevations in most of our cases is noteworthy.

Similarly, Tashakori et al.[11] evaluated 98 addicts (71% heroin-dependent, 7 subjects HIV positive) on methadone maintenance treatment and found liver function test results to remain in the normal range during the year following treatment. However, liver enzyme levels of HIV positive patients elevated shortly after methadone treatment and remained moderate afterwards.[11]

In a three-year long study, Kreek et al. assessed methadone hepatotoxicity in 214 patients (with or without hepatic disease) on high dose methadone maintenance treatment (80-120 mg daily). None of the 129 patients who completed the study showed signs of hepatotoxicity by methadone. Among these, 23% had a history of hepatitis and 25% were moderate to heavy alcohol consumers. Liver test abnormalities were reported in 57% of the subjects at the time of admission. Three years after the initiation of treatment, 51% of abnormalities were associated with hepatitis or alcohol consumption.[9] Although we did not consider existing liver and heart conditions and the consumption of alcohol or other drugs, the mentioned studies strongly confirm our findings.

ALP is a non-specific enzyme which is elevated in a number of disorders such as various bone, heart, and kidney diseases and also in cholestatic liver disorders and liver infiltration. Limitations of the present study included small sample size, the retrospective nature of the trial, and the inability to include other liver tests and tests related to viral hepatitis. Further prospective studies with larger sample size encompassing various tests for evaluating liver function, viral hepatitis, alcohol consumption and other drugs (affecting liver function or causing cholestatic liver) are required to gain a more accurate insight into the effects of methadone on liver. However, despite various limitations, this study indicated significant effects of methadone on patients' ALP levels. Absence of obvious effects on liver transaminases (ALT, AST) may suggest

cholestatic (obstructive) liver damage by methadone.

Conflict of Interest: The Authors have no conflict of interest.

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مقاله پژوهشی

تأثیر متادون بر آنزیم‌های کبدی در بیماران تحت درمان نگهدارنده با متادون

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چکیده

مقدمه: در حال حاضر متادون شایع‌ترین داروی مورد استفاده در درمان کوتاه مدت و به خصوص طولانی مدت ترک اپیوییدها می‌باشد. همچنین باورهای بیماران در خصوص اثرات منفی متادون بر عملکرد ارگان‌ها به ویژه کبد در همکاری آنان برای مصرف دارو تأثیرگذار است. این مطالعه با هدف، بررسی تأثیر متادون بر آنزیم‌های کبدی در بیماران تحت درمان نگهدارنده با متادون انجام شد.

روش‌ها: مطالعه حاضر به صورت گذشته‌نگر بر روی ۹۴ بیمار تحت درمان نگهدارنده با متادون در کلینیک MMT (Methadone maintenance treatment) بیمارستان شهید بهشتی کرمان انجام شد. آنزیم‌های کبدی بیماران هر ۶ ماه یک بار از ابتدای ورود به کلینیک MMT تا پایان ماه ۲۴ ثبت شد و نتایج بر اساس ارتباط سطوح آنزیم‌های کبدی و سن و جنس و دوز متادون مصرفی استخراج شد. جهت تجزیه و تحلیل داده‌ها از مدل Logistic regression با طرح داده‌های تصادفی استفاده شد.

یافته‌ها: مقدار ALT (Alanine transferase) در ۴ نفر (۴/۳ درصد) و AST (Aspartate transferase) در ۳ نفر (۳/۲ درصد) در ماه ۲۴ (آخر) بالاتر از حد طبیعی بود، اما ۴۶ نفر (۵۰ درصد) در ماه ۲۴ سطوح ALP (Alkaline phosphatase) غیر طبیعی داشتند؛ از این تعداد، ۲۶ نفر زیر ۴۰ سال و ۲۰ نفر بالای ۴۰ سال بودند (میانگین سنی افراد با ALP غیر طبیعی، ۳۹/۹ سال بود و میانگین دوز مصرفی متادون در آن‌ها ۱۹/۵ cc (Each cc of methadone = ۵ mg) بود.

نتیجه‌گیری: نتایج مطالعه حاضر حاکی از تأثیر چشمگیر متادون بر ALP می‌باشد که نشانه احتمالی الگوی آسیب کلستاتیک (انسدادی) متادون بر کبد است. برای تأیید نتایج این مطالعه، مطالعات بیشتر به صورت آینده‌نگر و با حجم نمونه بیشتر و همچنین در نظر گرفتن سایر داروهای مصرفی و بیماری‌های کبدی قبلی توصیه می‌شود.

واژگان کلیدی: متادون، سوء مصرف مواد، کبد، ALT، AST، ALP

مجله اعتیاد و سلامت، سال چهارم، شماره ٤-٣، تابستان و پاییز ۱۳۹۱

تاریخ دریافت: ۹۰/۱۲/۳ **تاریخ پذیرش:** ۹۱/۲/۳۱

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